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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/820,560	04/08/2004	Patrick Midoux	410.015-Reissue	8665

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HEDMAN & COSTIGAN P.C.
1185 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

EXAMINER	
KELLY, ROBERT M	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 10/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/820,560	MIDOUX ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments and arguments of 9/19/05, 5/11/05, and 2/4/05 are all entered.

Claims 1, 2, and 11 are amended.

Claims 1-16 are presently pending and considered.

Examiner Reassignment

Examiner Nguyen has been promoted to SPE of Art Unit 1633; hence, this Application has been reassigned. Examiner Robert M. Kelly, of Art Unit 1633, is continuing the prosecution of this Application. Please address all future correspondence accordingly. The Examiner's information, as well as that of the SPE of Art Unit 1633 is provided at the end of the Action.

Effecting Claim Amendments

It is noted that the amendment of 2/4/05 contained proper claim markings, but did not identify the claims with the parenthetical expression of "amended", "twice amended", etc, as required by 37CFR 1.173. Moreover, subsequent amendments of 5/11/05 and 9/19/05 do not comply with proper markings, and instead make amendments as if prior non-entered amendments (i.e., 2/4/05 and 5/11/05) have been entered. The proper amendment practice during reissue is to always mark the difference between the claims as presently-presented versus the claims that were issued. The Application cannot be allowed if 37 CFR 1.173 is not complied with.

In addition, the Examiner apologizes for the non-responsive amendment of 5/5/05. It appears that Applicant had properly marked-up the claims, but the pre-examination review mistook this Application for a normal application subject to section 1.121 of the CFR, rather than 1.173.

However, Applicant's claim amendments contain many errors deviating from the original claim language in such a way, and not indicating changes, that the Examiner would consider such to be inadvertent error. For example, claim 11, as amended in the amendment of 9/19/05 recites the limitation "the said polylysine can be substituted by a molecular with a recognition signal". It is obvious that this is an error, as there is no such thing as a molecular, but the term molecule was originally used, and therefore, it is the reasonable interpretation of the Examiner that such amendment was not intended. Moreover, it is asserted that each limitation, described below, which deviates from the issued patent claims is considered the reasonable interpretation considering the Applicant's amendments and apparent intent. Further, this appears to be the very reason that Applicant wishes reissue, according to Applicant's arguments (below). It would behoove Applicant to pay more particular attention to their claim terminology.

However, in order to make clear the amendments as the Examiner understands them, and to allow Applicant to ascertain that the proper amendments have been entered, the claims considered to be amended are restated, with markings to indicate differences between the claims as issued and the presently presented claims. Applicant is required to present a correct amendment of the Claims. Claims 1, 2, 11, and 16 (16 is new to the reissue) are listed.

Claim 1. A complex comprised of at least one negatively charged nucleic acid and at least one positively charged polymeric conjugate with the bond therebetween being electrostatic in nature,

the polymeric conjugate containing a polylysine formed from monomers having free NH_3^+ groups,

at least 10% of free NH_3^+ groups of the said polylysine are substituted by residues which are protonated in a weakly acid medium causing destabilization of cell membranes,

and optionally at least one free NH_3^+ group of the said polylysine is substituted by a molecule with a recognition signal recognized by a cell membrane receptor,

with the proviso that all the free NH_3^+ groups of the said [polysine]polylysine make up least 30% of the number of monomers of the skeleton of the polymeric conjugate wherein said residues causing destabilization of cell membrane in a weakly acid medium [belong to the family of]are selected from the group consisting of family of compounds having an imidazole nucleus, pterines, pyridines and quinolines of the formula: **FORMULA UNCHANGED**

in which R_1 is hydrogen, R_2 is $-(CH_2)_n-CO_2-H$, X is hydrogen or chloride and n is an integer from 1 to 10, wherein said recognition signal is selected from the consisting of:

a) simple osides selected from the group consisting of α or β conformers of 2-deoxy, 2-amino or 2-deoxy, 2-acetamide neutral monosaccharides; α or β conformers of glycuronic acid derivatives of neutral monosaccharides, α or β conformers of L-iduronic acid, of keto-deoxy-octonic acid, of N-acetyl neuraminic acid or of N-glycoloyl-neuraminic acid; and α or β conformers of neutral 6-deoxy monosaccharides;

b) a disaccharide selected from the group consisting of lactose and mannopyranosyl α-6-mannopyranose,

c) complex osides selected from the group consisting of $Lewis^a$, $Lewis^b$, $Lewis^x$, oligomannosides and oligolactisoamines and

d) peptides.

2. The complex of claim 1 wherein said quinolines are selected from the group consisting of 7-chloro-4-(amino-1-methyl-butylamino)-quinoline, N^4-(7-chloro-4-quinolinyl)-1,4-pantanediamine, 8-(4-amino-1-methylbutylamino)-6methoxyquinoline (primaquine), N^4-(6-methyoxy-8-quinolinyl)-1,4-pentanediamine, histidine and pyridines selected from the group consisting of nicotinic acid and quinolenic acid and pterines.

11. Positively charged polymeric conjugate containing a polylysine formed from monomers having free NH_3^+ groups,

at least 10% of free NH_3^+ groups of the said polylysine are substituted by residues which are protonated in a weakly acid medium causing destabilization of cell membranes,

and optionally some of the free NH_3^+ group of the said polylysine can be substituted by a molecule with a recognition signal recognized by a cell membrane receptor,

with the proviso that all the free NH_3^+ groups of the said polylysine make up least 30% of the number of monomers of the skeleton of the polymeric conjugate,

wherein said residues causing destabilization of cell membrane in a weakly acid medium [belong: to the family of]are selected from the group consisting of family of compounds having an imidazole nucleus, pterines, pyridines and quinolines of the formula: **FORMULA UNCHANGED**

in which R_1 is hydrogen, R_2 is $-(CH_2)_n-CO_2-H$, X is hydrogen or chloride and n is an integer from 1 to 10, wherein said recognition signal is selected from the consisting of:

simple osides selected from the group consisting of α or β conformers of 2-deoxy, 2-amino or 2-deoxy, 2-acetamide neutral monosaccharides; α or β conformers of glycuronic acid

derivatives of neutral monosaccharides, α or β conformers of L-iduronic acid, of keto-deoxy-octonic acid, of N-acetyl neuraminic acid or of N-glycoloyl-neuraminic acid; and α or β conformers of neutral 6-deoxy monosaccharides;

a disaccharide selected from the group consisting of lactose and mannopyranosyl α-6-mannopyranose,

complex osides selected from the group consisting of Lewis^{a}, Lewis^{b}, Lewis^{x}, oligomannosides and oligolactisoamines and

peptides.

16. The complex of claim 1 wherein the residue causing destabilization of cell membrane in a weakly acid medium is alkylimidazole of 1 to alkyl carbon atoms.

If Applicant disagrees that these are the amendments presently being considered, in comparison to the originally-issued claims in U.S. Patent No. 6,372,499, the Examiner requests notification and explanation of how the claims should differ. Nonetheless, the next action will not preclude finality, as it is Applicant's inability to properly address the amendments which have caused the Examiner's interpretation to be considered the reasonable interpretation.

Specification

The specification remains objected to because the first paragraph of the specification regarding the cross-reference information needs to be updated to reflect the relationship between this reissue application and the issued patent. (Official Action of 11/12/04, p. 2.)

Applicant is again notified that any subsequent amendment to the specification and/or claims must comply with 37 CFR 1.173.

35 USC 251 – recapture of surrendered subject matter

Claims 1-10 and 16 remain, and claims 11-15 are newly rejected under 35 USC 251 as being an improper recapture of claimed subject matter surrendered in the application for the patent upon which the present reissue is based, as provided in the Official Action of 11/12/04, pp. 3-5.

Response to Argument – recapture of surrendered subject matter

Applicant's argument of 2/4/05 has been fully considered but is not found persuasive.

Applicant argues that the after-final response of 7/17/01 attempted to overcome all the 35 USC 112 rejections, but, with regard to the art rejections (1) Applicant argued against the art rejections; and (2) did not indicate any deletion of references to histidine or residues with an imidazole nucleus conjugated to polylysine. Moreover, the Examiner did not enter the claims as presented after-final in the Advisory Action of 7/31/05, but indicated amendments that would overcome the new rejections that would be present under 35 USC 112. Essentially, Applicant is arguing that they did not give up the subject matter which is the subject of this rejection because they did not indicate in the claims that such subject matter was cancelled, and because they presented arguments against the Examiner's art rejection.

Such is not persuasive. Applicant's proposed amended claims were not entered, but the Examiner indicated that such claims would overcome various rejections, including the rejections under 35 USC 103 (Advisory Action of 7/31/05, No. 3, section labeled "NOTE:"). Hence, it is

apparent that the Examiner withdrew the rejection based on Applicant's proposed amendment, which did not include the subject matter presently being prosecuted. Moreover, Applicant is responsible to review their own claims, and other forms of recourse were present for Applicant to obtain further prosecution of the cancelled subject matter, including filing an RCE or continuation application. Applicant has already received consideration of this subject matter, and chose not to pursue it further, and arguing for further consideration after a decision has been made as to the allowable subject matter is not a proper venue for reissue application proceedings.

Applicant argues that the omission of histidine was in advertent omission, and was not intended to be given up, and that the amendment to claim 1 merely incorporates this language. (Applicant's argument of 2/4/05, pp. 15-16, paragraph bridging).

Such is not persuasive. While Applicant may well not have intended to give up the subject matter, Applicant did give up the subject matter, and the Examiner did indicate that the prior art rejections would be overcome by the amendment, not by the argument (Advisory Action of 7/31/05, No. 3, section labeled "NOTE:"). Moreover, subsequent to the advisory action, no amendment includes the subject matter which Applicant gave up until the amendment after issuance of 5/11/05. Applicant is responsible for understanding the prosecution of the Application, and simply arguing that something was a mistake after a decision has been rendered does not allow Applicant to recover subject matter that has been given up. Applicant had other avenues to recapture such subject matter, including RCE or continuation, but Applicant did not choose to pursue those avenues. The only conclusion that the Examiner can reach is that Applicant did give up such subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10 remain, and claims 11-15 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over either FR-A271316 (D1) or Midoux, et al. (U.S. Patent No 5,733,762, wherein Erbacher and Roche-Degremont constitute as another inventive entity, entire document), taken with Wang, et al. (D3).

It is noted that Applicant has now amended the composition of claim 11 for the polypeptide to include the same histidine residues, and as such, claims 11-15 are subject to the same rejection. To wit, if the composition with the polynucleotide is obvious, the composition without it is obvious, as one would make the composition as a precursor to the transfection composition.

Response to Argument – obviousness

Applicant's arguments of 2/4/05, and referenced argument of 7/17/01, have been fully considered but are not found persuasive.

Applicant argues that the Wang reference, while suggesting that histidine is an alternative fusion means, Applicant has shown it useful in living cells, and Wang only demonstrates its use in polyhistidine destabilized phosphatidylserine liposomes. Hence, Applicant argues that it is unexpected that polyhistidine would destabilize living cells. Moreover, Applicant argues that the protonated histidine would interact with the polynucleotide, and hence the Artisan would expect it to preclude destabilization of the membrane. (Applicant's argument of 7/17/05, pp. 15-16, paragraph bridging.)

Such is not persuasive. With regard to Applicant's argument as to their demonstration in cells, versus Wang's demonstration, the Examiner fails to understand why one would doubt the efficacy of Wang's demonstration producing a reasonably-predictable result, versus Applicant's further demonstration of what Wang predicts. Secondly, if Applicant's argument with regard to the interaction of protonated histidine with the DNA were correct, one would expect similar circumstances for any similarly charged molecule. Wang demonstrates fusion of lipids, in the presence of acidic phospoholipids (ABSTRACT). Hence, why did the histidine not interact with

the phospholipids instead of causing fusion? Therefore, Applicant's argument is not considered persuasive.

Applicant argues that D3 is limited to histidine polymers, while Applicant's claims are drawn to histidine groups bound to lysine. Hence, Applicant argues, the claims are not obvious. (Applicant's argument of 7/17/05, p. 16, paragraph 2.)

Such is not persuasive. Wang is not used alone in this obviousness rejection, but in combination with either one of two other documents, which both teach conjugation of such groups onto lysine (e.g., Midoux, U.S. Patent No. 5,733,762, ABSTRACT). The combination of the references certainly does then suggest the substitution of histidines onto lysine.

Applicant further rehashes the prosecution history of the original Application of 09/297,519, paralleling arguments made in the above-addressed arguments to the recapture of relinquished subject matter (Applicant's argument of 2/4/05, p. 17).

Such is not persuasive for reasons given in the above-addressed arguments. Applicant has already had adjudication of this patent, and had other opportunities to obtain reconsideration of the present subject matter.

Hence, the rejections remain.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-10 and 16 remain, and claims 11-15 are newly rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9-15 of U.S. Patent No. 5,733,762 in view of D3. Although the conflicting claims are not identical, they are not patentably distinct from each other, for reasons of record.

It is noted that Applicant has newly amended claims 11-15 to encompass the same polypeptides, in absence of the polynucleotide, however, such is obvious because it is a necessary precursor to making the compositions for transfection.

Response to Argument – Double Patenting

Applicant's argument of 7/17/05 has been fully considered but is not found persuasive.

Applicant argues that the rejection is essentially one of the references in the rejections under 35 USC 103, and thus the same arguments to the same reference (D1). Hence, Applicant argues, no terminal disclaimer is required, and no double patenting rejection applies. (Applicant's argument of 7/17/05, p. 17.)

Such is not persuasive. As has been stated above, Applicant's arguments with regard to D1 are not found persuasive, and therefore, they are similarly not persuasive here.

The rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's claim 2 limits the quinolines of claim 1, drawn to a specific structure genera to, *inter alia*, histidine, nicotinic acid, quinolenic acid, and pterines. It is unclear how a histidine may be a quinoline, how quinolenic acid may be a quinoline, and how a pterine may be a quinoline. Specifically, as in Applicant's specification, quinolines of the invention are represented by the formula given on col. 9, first paragraph, of U.S. Patent No. 6,372,499. However, pterines and pyridines of the invention have distinct structural requirements (Id., paragraphs 2-3). Moreover, the art recognized term "quinolinic acid" is equivalent to one of Applicant's pyridines (2,3-dicarboxyl pyridine, Merck Index, 11th Ed., No. 8102).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's claims encompass the genera of quinolines. As was stated in the rejections due to indefiniteness, Applicant is claiming structures that are not quinolines as being within the genera of quinolines. Hence, Applicant's description does not convey to the Artisan that possession of the genera of quinolines is possessed, much less what is actually encompassed by quinolines in the first place.

Conclusion

No claim is allowed.

Because the Examiner added new grounds of rejection, i.e., written description and indefiniteness, this action is non-final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert M. Kelly, Ph.D.
Examiner, USPTO, AU 1633
2C55 Remsen Building
(571) 272-0729

DAVE TRONG NGUYEN
SUPERVISORY PATENT EXAMINER